Hematology:

Percent Change From Control in Hematological Parameters			
	HD ♀	MD ♂	HD ♂
RBC			
Week 5	—	—	↓26
Week 9	—	↓36	↓26
Week 13	—	↓10	↓28
Recovery	—	—	—
HGB			
Week 5	↓15	—	↓23
Week 9	↓16	↓10	↓20
Week 13	↓14	↓9	↓22
Recovery	—	—	—
HCT			
Week 5	—	—	↓23
Week 9	↓19	↓12	↓23
Week 13	↓16	↓10	↓24
Recovery	↑4	—	—
Absolute lymphocyte count			
Week 5	—	—	↓41
Week 9	—	—	↓49
Week 13	—	—	—
Recovery	—	—	—
Absolute monocyte count			
Week 5	—	—	—
Week 9	—	—	↓46
Week 13	—	—	↓25
Recovery	—	—	—

Clinical chemistry:

Percent Change From Control in Clinical Chemistry Parameters		
	HD ♀	HD ♂
Phosphorus		
Week 5	↓27	↓26
Week 9	—	↓23
Week 13	↓34	↓22
Recovery	—	—
Cholesterol		
Week 5	—	↓34
Week 9	—	↓37
Week 13	—	↓39
Recovery	—	—

Urinalysis: No treatment-related effects

Organ weights: No treatment-related effects

Gross pathology: No treatment-related macroscopic findings

Histopathology: No treatment-related histopathological findings

Toxicokinetics:

Table 4.6-1. Summary of toxicokinetic data for CGP 57148B

	3 mg/kg/day		15 mg/kg/day		75 mg/kg/day	
	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)
MALES:						
Days 1/2	214 ± 155	37.2 ± 34.5	1650 ± 1240	216 ± 170	16000 ± 5390	1210 ± 325
Days 91/92	230 ± 107	32.4 ± 18	1450 ± 1710	178 ± 236	15800 ± 5730	1080 ± 384
FEMALES:						
Days 1/2	218 ± 83.0	40.9 ± 20.6	2340 ± 1340	310 ± 152	15000 ± 4500	1230 ± 287
Days 91/92	286 ± 61.1	44.6 ± 13.2	1960 ± 291	206 ± 69.0	15600 ± 4610	1280 ± 143

Table 7.1-11 Dose Normalized AUC_{0-24h} and C_{max}

	AUC_{0-24h} (ng h/mL)				C_{max} (ng/mL)			
	Male		Female		Male		Female	
Dose (mg/kg/day)	Day 1	Day 91	Day 1	Day 91	Day 1	Day 91	Day 1	Day 91
3	71.3	72.7	78.7	96.3	12.4	13.8	10.8	14.9
15	110	156	97	131	14.4	20.7	11.7	13.7
75	213	200	211	208	16.1	16.4	14.4	17.1

Summary of individual study findings:

Daily dosing daily for 13 weeks with imatinib at doses of 3, 15 and 75 mg/kg/day was not lethal in this monkey study. The highest dose administered did cause gastrointestinal effects, as evidenced by emesis in 9/10 animals. The toxicokinetic data indicates that the emesis seen in the HD monkeys did not interfere with the absorption of the administered dose of drug, as the expected increase in AUC with higher doses was evident. Four animals, two of each sex, at this dose did show a decrease in body weight during the first 3 weeks, all except one female began gaining weight after week 3. That HD female weighed 7% less at the end of the 13-week dosing than at the beginning of the testing. Hematological changes were seen, primarily in the HD animals, and had resolved by the end of the recovery period. Predominately, these changes included red cell changes. Red blood cell count, hematocrit and hemoglobin were all significantly decreased by 20-28% from control in the HD males during the 13-week administration. More modest decreases were seen in the HD females in hematocrit and hemoglobin, 14-19% less than control. These red cell changes could explain the pale gums seen in the HD monkeys, but even at the end of the recovery period, when the red cell parameters were not significantly lower than control, the pale gums were seen in 3/4 monkeys.

White blood cell parameters, mainly absolute monocyte and lymphocyte counts, were significantly decreased in the HD male monkeys. These values returned to normal by the end of the recovery period.

Toxicokinetic data show no sex differences in the exposure levels of STI571 and no accumulation of the drug over the 13-week dosing schedule. The AUC_{0-24h} was overproportional to the dose of STI571 administered. The C_{max} increased proportionally with higher doses.

STI571, administered daily to monkeys in doses of 3 and 15 mg/kg/day, was tolerated well by the animals with minimal toxicity. The high dose, 75 mg/kg/day, had hematological

effects, increased incidence of emesis, and caused pale gums and skin in the majority of animals. The toxicities, with the exception of the pale skin and gums, were not noted at the end of the recovery phase.

The highest dose tested was not tolerated well by the monkeys, based on the emetic effects. This dose was chosen based on the results of the 2-week monkey study with oral STI571 administration (Test 977090). In that study, 100 mg/kg/day caused emesis and minimal to moderate centrilobular vacuolation of the liver. It was the sponsor's belief that the high dose for this study, 75 mg/kg/day, would cause 'definitive toxicological/pharmacological signs'. More relevant toxicological data may have been obtained with testing higher doses for the longer 13-week period. Continuing to use 100 mg/kg/day as the high dose in the long-term studies seems warranted. Emesis seems to have been their dose-limiting toxicity in the dose range finding study. Any other signs of STI571 toxicity at this dose were minimal. The results of the dose range finding study do not seem to justify the lower high dose tested in this 13-week study.

Study title: 39-week oral gavage (b.i.d.) toxicity study in monkeys with a 4-week recovery period.

Key study findings: Testicular changes were seen at all dose levels tested, so no NOEL dose was seen. HD animals showed clinical signs of gastrointestinal effects of the drug treatment. One HD female monkey died from STI571 toxicity. STI571 may have increased susceptibility to the malarial parasite that is common in African and Asian monkeys.

Study no:	Test 007048
Volume #, and page #:	Volume 3.1, page 1
Conducting laboratory and location:	Novartis Pharmaceuticals Corp., East Hanover, NJ
Date of study initiation:	3 April 2000
GLP compliance:	Compliance included and signed
QA report:	yes (X) no ( )
Drug, lot #, and % purity:	STI571 mesylate, lot# 9923006, 99.9% pure
Formulation/vehicle:	Purified water, USP

Methods (unique aspects): No unique aspects

Dosing:

Species/strain:	Monkey/Cynomolgus
#/sex/group or time point:	4/sex/group
Satellite groups used for toxicokinetics or recovery:	2/sex HD monkeys for recovery phase
Age:	Approximately 2.5 – 5 years
Weight:	2.8 – 4.4 kg ♂ and 2.4 – 4.3 kg ♀
Doses in administered units:	0, 15, 30 and 80 mg/kg/day – divided doses – b.i.d.
Route, form, volume, and infusion rate:	Oral, gavage, 2 mL/kg volume

Observations and times:

Clinical signs:	Once daily pre-test and recovery; at least 3 times daily during dosing
Body weights:	Once weekly during dosing and recovery
Food consumption:	Estimated daily
Ophthalmoscopy:	During pretest, week 26 and end of dosing
EKG:	Pretest and after last dose during week 39
Hematology:	Pretest and weeks 7, 13, 17, 23, 31, 35, 39 and recovery week 4
Clinical chemistry:	Pretest and weeks 7, 13, 39 and recovery week 4
Urinalysis:	Pretest and weeks 7, 13, 39 and recovery week 4
Gross pathology:	At scheduled sacrifice – end of 39 weeks or after 4 weeks recovery for 4 HD monkeys
Organs weighed:	Adrenal, brain, heart, kidney, liver, ovary, pituitary, prostate, spleen, testis, thyroid, uterus
Histopathology:	At scheduled sacrifice – end of 39 weeks or after 4 weeks recovery for 4 HD monkeys
Toxicokinetics:	Day 1 (between 2 dosings), weeks 4 and 39

Results:

Mortality: HD ♀ euthanized on Day 16 from STI571 toxicity

Clinical signs:

Frequency of Clinical Signs

	30 mg/kg		80 mg/kg	
Soft feces/diarrhea	1/6 ♂	—	5/6 ♂	1/5 ♀
Reduced feces	—	—	3/6 ♂	1/5 ♀
Increased emesis	—	—	1/6 ♂	3/5 ♀

Body weights: Euthanized HD ♀ - 15% body weight loss by day 16
HD ♂ - decreased overall weight gain throughout study – others in this group averaged 0.9g weight gain to this animal's 0.3g gain

Food consumption: 3/6 HD ♂ - consumed less than 50% of the food given them
2/5 HD ♀ - consumed less than 25% of the food given them
During recovery – consumed 75-100% of food given

Ophthalmoscopy: No treatment-related effects

Electrocardiography: No treatment-related effects

Hematology:

Percent Change From Control in Hematological Parameters

	MD ♀	HD ♀	MD ♂	HD ♂
RBC				
Week 7	↑1	↓18	↓8	↓19
Week 13	↓9	↓22	↓8	↓25
Week 17	↓5	↓25	↓11	↓21
Week 23	↓3	↓22	↓13	↓25
Week 31	↓3	↓18	↓9	↓23
Week 35	↓0.4	↓14	↓8	↓21
Week 39	↓4	↓20	↓1	↓23
Recovery	—	↓5	—	↓3
HGB				
Week 7	↓2	↓16	↓5	↓20
Week 13	↓5	↓16	↓5	↓20

Week 17	↓4	↓17	↓8	↓18
Week 23	↓6	↓17	↓10	↓24
Week 31	↓2	↓14	↓4	↓18
Week 35	↓2	↓13	↓6	↓21
Week 39	↓2	↓14	↓3	↓17
Recovery	—	↑2	—	↓0.8
HCT				
Week 7	↑3	↓16	↓5	↓17
Week 13	↓7	↓19	↓5	↓22
Week 17	↓4	↓20	↓9	↓17
Week 23	↓0.8	↓18	↓8	↓19
Week 31	↓2	↓16	↓6	↓19
Week 35	↓1	↓11	↓4	↓16
Week 39	↓2	↓15	↓5	↓21
Recovery	—	↑2	—	↓2
MCV				
Week 7	↑2	↑3	↑3	↑2
Week 13	↑0.3	↑4	↑3	↑5
Week 17	↑1	↑7	↑3	↑5
Week 23	↑3	↑6	↑5	↑7
Week 31	↑0.5	↑4	↑2	↑5
Week 35	↓0.5	↑4	↑4	↑5
Week 39	↑1	↑6	↑2	↑3
Recovery	—	↑7	—	↑1
MCH				
Week 7	↓0.4	↑4	↑3	↑5
Week 13	↑2	↑7	↑2	↑6
Week 17	↑1	↑7	↑3	↑8
Week 23	—	↑7	↑4	↑8
Week 31	↑1	↑6	↑5	↑9
Week 35	↓0.4	↑4	↑2	↑8
Week 39	↑2	↑8	↑4	↑6
Recovery	—	↑8	—	↑2

Clinical chemistry: Minimal decreases in serum albumin – MD and HD monkeys
Means were never more than 9% lower than controls

Urinalysis: No treatment-related effects

Organ weights: ↑ liver weights in HD monkeys when compared to control
- ♂ at week 39 – ↑23%
- ♂ at end of recovery – ↑31%
- ♀ at week 39 – ↑28%
- ♀ at end of recovery – ↑30%

↓ testis weights – HD ♂ compared to control – ↓41%

Gross pathology: 1/4 HD ♂ and 1/2 HD ♂ recovery monkeys - small thyroid
immature/degenerated testis – 1/4 LD, 2/4 MD, 2/4 HD

Histopathology: Some histopathological findings due to the malarial parasites, addressed in the following summary.

Some histopathological findings due to a fatal fasting syndrome in the euthanized monkey, also in the summary.

	LD		MD		HD	
Observation	♂	♀	♂	♀	♂	♀
[illegible], hepatocellular, centrilobular	—	—	—	3/5	3/4	3/4
[illegible] pigment, Kupffer cell	1/4	1/4	—	1/4	4/4	4/4
[illegible] pigment, Kupffer cell, centrilobular	—	—	1/4	—	4/4	2/4
[illegible], mononuclear	2/4	2/4	3/4	3/4	3/4	3/4
[illegible], interstitial	—	—	—	—	2/4	—
[illegible], interstitial, focal	1/4	—	—	1/4	—	2/4
Cast, tubular	—	—	—	1/4	2/4	2/4
Lymphocytosis				5/5	5/5	—
[illegible] atrophy				—	—	5/5
Histiocytosis				—	5/5	5/5
Hyperplasia, lymphoid	2/4	2/4	3/4	3/4	2/4	1/4
Pigment, macrophage	1/4	1/4	2/4	4/4	2/4	2/4
[illegible] lymph node Pigment, macrophage	3/4	2/4	3/4	—	4/4	2/4
[illegible] Mineralization	NA	2/4	NA	—	NA	4/4
[illegible] gland Ectopic thymus	2/4	2/4	—	1/4	2/4	4/4

Toxicokinetics:

Table 2.1-1. Toxicokinetic parameters for STI671 in plasma

		Day 1/2		Week 4		Week 39	
	Dose (mg/kg/day)	Cmax (ng/mL)	AUC_{0-24h} (ng/mL*h)	Cmax (ng/mL)	AUC_{0-24h} (ng/mL*h)	Cmax (ng/mL)	AUC_{0-24h} (ng/mL*h)
Male	15	139	1130	113	1180	107	1230
	30	369	2420	254	2800	289	2800
	60	1378	12900	919	14100	1184	14300
Female	15	128	1280	110	1340	143	1360
	30	386	3080	423	3650	344	3720
	60	1560	14800	949	15900	1126	16100

Table 2.1-2. Dose normalized TK parameters

	Dose	Day 1/2		Week 4		Week 39	
	(mg/kg/day)	Cmax*	AUC_{0-24h}**	Cmax*	AUC_{0-24h}**	Cmax*	AUC_{0-24h}**
Male	15	9.27	75.3	7.53	78.7	7.13	82.0
	30	12.0	80.7	8.47	86.7	9.63	86.7
	60	17.2	161	11.5	176	14.8	179
Female	15	8.53	85.3	7.33	89.3	9.53	90.0
	30	13.3	103	14.1	118	11.5	124
	60	19.5	185	11.9	199	14.1	201

* Units: (ng/mL)/(mg/kg/day)

** Units: (ng/mL*h)/(mg/kg/day)

Summary of individual study findings:

STI571 dosing to cynomolgus monkeys at the high dose of 80 mg/kg/day yielded clinical signs of gastrointestinal effects in the majority of the monkeys. Emesis, reduced feces, and diarrhea were seen in many of these HD animals. The emesis did not affect the intake of drug, based on the AUC data obtained in the toxicokinetics. The AUC from the high dose monkeys shows no marked decrease, as would be expected if the emesis was limiting the amount of drug absorbed. One HD female monkey was euthanized moribund from STI571 toxicity. Prior to sacrificing the animal was not eating, had persistent emesis and fecal changes, and had lost 15% of body weight. The severe emesis and dehydration were consistent with chemistry findings of hyponatremia and hypochloridemia. Hepatocellular and renal tubular vacuolation seen microscopically were consistent with renal and hepatic lipidosis, seen in monkeys with a fatal fasting syndrome due to anorexia, and therefore not directly due to STI571 toxicity.

Hematological effects were seen at the 30 and 80 mg/kg/day doses. Various forms of *Plasmodium sp* were present in 2/4 males and 2/4 females at the MD level, and 6/6 males and 3/5 females at the HD level. This was also seen in 2/4 LD males. It is possible that the red blood cell parameters were low in the MD and HD animals because of the red cell destruction effects of the malarial parasites. These effects are indirectly attributed to the test compound. It is possible that administration of STI571 permitted proliferation of the parasite, which is common in primates bred in Asia and Africa but rarely detectable in a blood film of a clinically healthy animal. There were histological changes in the liver, spleen and bone marrow believed to be due to the malarial infection. These included malarial pigment in the liver and spleen and lymphoid and reticulum cell hyperplasia of the spleen.

Histological changes and decreased weights of the testes were due to the STI571 treatment. Decreased tyrosine kinases have been shown to cause testicular degeneration in rats. Decreased testicular weights were seen with STI571 in the breeding rats used in the fertility study.

There is some indication of histological effects in the kidney in this study, as has been seen in monkeys in a two-week, b.i.d. administration study (Test 007019). The 2-week study was not reviewed in detail. In that study, focal tubular mineralization was seen in 3/4 monkeys given 150 mg/kg/day for 6 days with a reduction to 100 mg/kg/day for the remaining 8 days. Two of these HD monkeys had nephrosis, and one was euthanized on day 6 with nephrosis being the probable cause of morbidity. No other notable findings were observed in this dose range finding study. The lack of any clinical chemistry parameters of kidney toxicity in the 39-week study does not disprove the potential for renal toxicity, as the histological damage can be seen long before the clinical chemistry effects appear.

Toxicokinetic data shows no difference between male and female monkeys for C_{max} or $AUC_{0\text{-}24h}$ in this study. There was a dose effect on C_{max} or $AUC_{0\text{-}24h}$, though both parameters were slightly overproportional to the STI571 dose. Accumulation of the drug does not appear to be occurring as seen by a comparison of the first dose to the last dosing on week 39.

All three doses tested yielded some clinical or toxicological effects in the monkey. The lowest dose, 15 mg/kg/day, was devoid of the hematological and gastrointestinal effects seen at the two higher doses. These effects were more severe at the HD of 80 mg/kg/day. Testicular degeneration was seen in all doses, so there is no NOEL for STI571 in this study.

Doses for this study were chosen based on the 13-week study results and preliminary data from the 2-week b.i.d. study in monkeys with doses of 20, 75 and 150 mg/kg/day. The high dose was reduced to 100 mg/kg/day after 6 days because of the clinical signs, which included diarrhea, emesis and body weight loss. While the data from this group of monkeys support a potential for renal toxicity with STI571, the lower dose used in the study reviewed here was not able to add any additional information regarding this toxicity. The question remains as to whether renal toxicity may have been seen if higher doses were tested. While the 150 mg/kg/day may have been too high, a dose of 100 mg/kg/day for the 39-week period could have given more information regarding this, as well as other toxicities.

Toxicology summary:

The multiple dose toxicity data are summarized in the following table. This table is a compilation of the toxicity data reviewed in IND[ ]and within the NDA. Repeated oral dosing of imatinib has been tolerated well in rats, dogs and monkeys. Doses of 90 mg/m^2/day in the rat, 600 mg/m^2/day in the dog and 360 mg/m^2/day in the monkey were not severely toxic when administered daily for periods of 13-39 weeks. The STD_{10} for the 13-week daily rat exposure was 360 mg/m^2/day. Target organs in the animal studies are epithelial and glandular tissues.

Summary of the Multiple Dose Toxicology Studies with Imatinib Mesylate

Species (Study #) N/sex/ Dose	Route Duration	Critical Doses	Daily dose mg/kg	Daily dose mg/m^2	SIGNIFICANT FINDINGS
Rat (96-6203) GLP N=5	gavage 14-days	Lethal	600	3,600	**3,600 mg/m^2/day**: 2/5 ♂ and 2/5 ♀ died; the rest were killed in moribund condition; clinical signs: general deterioration, salivation, dyspnea, ataxia, cyanosis, ↓activity, chromorhinorrhea and chromodacryorrhea, muscular hypotension, body cool to touch and dehydration; ↓ b.w.; ↓ food consum.; ↓ RBC parameters in MD ♂ (~9% by wk1 and ~30% by wk2); ↑ ALAT, ASAT and bilirubin; ↓ triG and CHOLEST.; abnormal gross findings in stomach, intestine, liver, lung, spleen, kidney, adrenal glands and prostate; abnormal microscopic findings in stomach, intestines, heart, pancreas, liver, kidneys, lung and trachea, thymus, spleen, LN, prostate, ovaries, uterus, adrenals, lacrimal, mammary, salivary, thyroid and parathyroid glands, and bone marrow.
		~STD_{10}	200	1,200	**≤ 1,200 mg/m^2/day**: no deaths, ↓ food consum.; ↑ ALAT, ASAT and bilirubin; ↓ TRIG and CHOLEST.; ↑ organ weight: adrenals, heart, kidneys, lungs and ovary; ↓ organ weight: thymus and prostate; gross abnormal findings in stomach; microscopic abnormal findings in stomach, pancreas, liver, kidneys, lung and trachea, thymus, spleen, LN, uterus, adrenal, mammary, thyroid and parathyroid glands, and bone marrow.

Rat (90-570) GLP N=10	i.v. 29 days	NOAEL	30	180	**180 mg/m²/day:** no death occurred; changes in organ weight: prostate: ↑16%; liver: ↑ 9% and spleen: ↓ 15%
Rat (96-6106) GLP N=10-15	gavage 13-weeks	STD_{10}	60	360	**360 mg/m²/day:** no drug-related death; swollen cheek was noted but no other clinical signs; ↓ RBC, HB, HCT (wk9 and 14); ↑ ALAT, ASAT and CHOL; ↑ organ w./b.w. ratio: adrenals, heart, kidneys, liver, ovary; ↓ organ w./b.w. ratio: spleen and prostate; abnormal gross findings: enlarged masseter muscle, discoloration of lacrimal glands, enlarged ovaries and black-brown foci in ovary; abnormal microscopic findings: hypercellularity, erythroid hyperplasia and granulocyte hyperplasia in bone marrow; hyperplasia and mineralization in kidneys and urinary bladder, ↑ mitosis in liver; plasma cell or lymphoid hyperplasia, hemorrhage and hemosiderosis in LN. **120 mg/m²/day:** ↓ RBC and CHOLEST.; ↑ organ w./b.w. ratio: adrenals in ♂, kidneys, liver, ovary; ; ↓ organ w./b.w. ratio: spleen and prostate in ♂; enlarged masseter muscle; abnormal microscopic findings: hypercellularity in bone marrow; hyperplasia in kidneys (♂), hyperplasia and mineralization in urinary bladder (♂), ↑ mitosis in liver (♀), plasma cell or lymphoid hyperplasia and hemorrhage in LN.
Rat (00-7033) GLP N=20-30	Gavage 26 weeks	NOAEL	50 15 5	300 90 30	**300 mg/m²/day:** no drug-related death; clinical signs – salivation/oral red substance (30/30 ♂) chromodacryorrhea (22/30 ♀), prominent eyes, perineal staining, red penile discharge (30/30 ♂), swollen appendage, swollen muzzle (30/30 ♂, 30/30 ♀), prominent eyes/oral red substance (29/30 ♀); ↓ body weights during recovery; ↓RBC, HB, HCT (♂ and ♀); ↓Plat (♂); ↑MCV, MCH, MCHC; ↓EOS, NEU (♂only), ↑WBC and EOS (♀ only); ↑ ALAT, ASAT; ↑ Total Protein, ALB, Glob (♀), ↓ CHOL (♀); ↑ heart, adrenal wt (♂ and ♀), ↑ adrenal in ♀ at recovery, ↑liver and thyroid wt (♂), ↑ovary, ↓ testis and spleen wt (♂), ↓pituitary wt (♀) – still seen at recovery; abnormal gross findings: enlarged masseter muscle, dark nodules in ovary, still seen at recovery; abnormal microscopic findings: hemorrhagic corpora lutea, cystic corpora lutea, and hemosiderophages in ovary – still seen at recovery, hypertrophy of masseter muscle – still seen at recovery, foamy macrophage lungs – still seen at recovery, eosinophilic macrophages of LN – still seen at recovery, atrophy of acinar cells in harderian gland – still seen at recovery, hyperplasia, renal pelvic epithelium, small foci of fibrosis in bone marrow, new bone formation, focal angiectasis adrenal cortex **90 mg/m²/day:** no drug-related death; clinical signs – salivation/oral red substance (13/20 ♂) chromodacryorrhea (2/20 ♀), prominent eyes, perineal staining, red penile discharge (10/20 ♂), prominent eyes/oral red substance (5/20 ♀); ↓ RBC (♂), ↑MCV, MCH (♂); ↑ heart and ↓ spleen wt in ♂; abnormal microscopic findings: atrophy of acinar cells in harderian gland, hyperplasia, renal pelvic epithelium, small foci of fibrosis in bone marrow.

					30 mg/m²/day: no death occurred; clinical signs salivation - oral red substance (2/20 ♂) chromodacryorrhea (6/20 ♀)
Dog (96-6204) GLP N=3	p.o. 14-days	NHSTD NOAEL	100 3	2,000 60	**2,000 mg/m²/day:** no death; occasional emesis; diarrhea: 3/3 ♂ and 1/3 ♀; salivation: 3/3 ♂ and 3/3 ♀; ↓ RBC, HB, HCT, WBC, ↑ fibrinogen; ↑ ALAT (7-12 ×), ASAT (2-3.6 ×), AP (88%); ↓ CHOLEST., total protein and ALB; ↑ organ w./b.w. ratio: adrenals, liver, kidneys, and ovary; ↓ organ w./b.w. ratio: thymus (♂), spleen and prostate; abnormal histopathology: hypercellularity in bone marrow, edema, fibrin thrombus and vasculitis in small and large intestines, transitional cell degeneration and hyperplasia in kidney, bileduct epithelium degeneration, hyperplasia and hypatocytic hypertrophy of the liver, hemorrhage and focal necrosis, ↑ mitosis in liver (♂); epithelium degeneration and hyperplasia of the gallbladder; epithelial vacuolar degeneration of stomach, hemosiderosis of spleen; lymphocytosis in spleen and LN **600 mg/m²/day:** ↓ RBC, HB, HCT, WBC, ↑ fibrinogen; ↑ ASAT (♂), ↓ CHOLEST. (16-28%); ↑ organ weight/b.w. ratio: adrenals (♂), liver (♂) and ovary; abnormal histopathology: hypercellularity in bone marrow, hemosiderosis of spleen
Dog (96-006) GLP N=3	i.v. 4-weeks	HNSTD	30	600	**600 mg/m²/day:** dermatitis: 1/3 ♀, diarrhea: 1/3 ♂ and 3/3 ♀; hypoactive: 1/3 ♀; lacrimation: 2/3 ♀; salivation: 1/3 ♀; reddened skin: 1/3 ♀; vomit: 2/3 ♂ and 3/3 ♀; ↓ b.w.; ↓ RBC, HB, HCT, WBC, NEUT; ↑prothrombin time; ↑ALAT; ↓ CHOL, TriG, total Bilirubin and ALB; ↓ testes weight; gross findings: thrombosis, perivascular fibrosis, necrosis and edema at injection sites. **200 mg/m²/day:** diarrhea: 1/3 ♀; hypoactive: 1/3 ♀; lacrimation: 1/3 ♀; ↓ RBC, HB, HCT.
Dog (96-6105) GLP N=3	p.o. 13-weeks	Lethal HNSTD NOAEL	100->50 30 3	2,000-> 1,000 600 60	**2,000/1,000 mg/m²/day:** 1/3 ♂ was killed in moribund condition; clinical signs: ataxia: 3/3 ♂, head shaking: 1/3 ♀, hyperemia: 3/3 ♂ and 3/3 ♀, pallor: 3/3 ♂, salivation: 3/3 ♂ and 3/3 ♀, diarrhea: 1/3 ♂ and 1/3 ♀, emesis, emesis with blood: 1/3 ♂, emesis with apparent compo.: 1/3 ♂ and 1/3 ♀, emesis with bile: 1/3 ♂ and 1/3 ♀, urine blood: 1/3 ♂, reddening of eyes: 3/3 ♂ and 3/3 ♀; ↓ food consumption (13-17%); ↓ RBC, HB, HCT and Reticulocytes; ↑ALAT (22-27 X), ASAT (4-7 X), AP (3-8 X); ↓ CHOLEST.(50-65%), TriG (30%), total protein (20%), ALB (20%) and α-globulin (20%); ↓ organ w./b.w. ratio: adrenals, spleen (♂), thyroid and testes; ↑ organ w./b.w. ratio: ovary and prostate; gross findings: clay gray colored testes, enlarged ovaries, yellow foci in liver; histology finding: pigment deposition in lung, kidney, liver, gall bladder, adrenals, bone marrow and LN, erosion in stomach, ileum and rectum, cryptal plug in cecum, colon and rectum; bile duct hyperplasia and vacuolation of liver, cholangitis, vasculitis and perivasculitis, peribiliary fibrosis of the liver, hypo- and hyper-cellularity of bone marrow, atrophy of thymus, cortex hypertrophy of adrenal and thyroid glands, ↓ spermatogenesis in testes, and cystic corpus luteum in ovary.

					600 mg/m²/day: clinical signs: ataxia: 3/3 ♂, eye discharge: 3/3 ♂, emesis with apparent compo.: 1/3 ♂, clinical signs: ataxia: 3/3 ♂, head shaking: 1/3 ♀, hyperemia: 3/3 ♂ and 3/3 ♀, pallor: 3/3 ♂, salivation: 3/3 ♂ and 3/3 ♀, eye discharge: 3/3 ♂ and 3/3 ♀, diarrhea: 1/3 ♂ and 1/3 ♀, emesis, emesis with blood: 1/3 ♂, emesis with apparent compo.: 1/3 ♂ and 1/3 ♀, emesis with bile: 1/3 ♂ and 1/3 ♀, urine blood: 1/3 ♂; ↓ RBC, HB, HCT; minor ↑ALAT (2X), ASAT (1.5 X); ↓ organ w./b.w. ratio: adrenals (♂), spleen , thyroid and testes; ↑ organ w./b.w. ratio: ovary and prostate; histology: pigment deposition in lung (♀), liver, and LN (♀); follicular atrophy of thyroid, hypo- and hyper-cellularity (♂) of bone marrow, oligospermia in testes, epididymides.
Monkey (98-7003) GLP N=3	Gavage 13 weeks	**NOAEL**	75 15 3	900 180 36	**900 mg/m²/day:** no death; clinical signs: emesis: 5/5 ♂ and 4/5 ♀, pale skin: 3/5 ♂ and 4/5 ♀ (4/4 recovery), pale gums 3/5 ♂ and 3/5 ♀ (3/4 recovery), ↓ body weight first 3 weeks, 2/5 ♂ and 2/5 ♀, 1♀ still decreased at week 13; ↓ RBC (♀ only), HB, HCT, Lymp (♀ only) and Mono (♀ only) ; ↓ CHOL (♀ only), ↓ P **180 mg/m²/day:** ↓ RBC, HB, HCT (♀ only) **36 mg/m²/day:** no drug-related effects
Monkey (00-7048) GLP N=18	Gavage 39 weeks (b.i.d.)		80 30 15	960 360 180	**960 mg/m²/day:** one ♀ euthanized moribund from STI571 toxicity; clinical signs: soft feces/diarrhea (5/6♂ and 1/5 ♀), reduced feces (3/6 ♂ and 1/5 ♀) increased emesis (1/6 ♂ and 3/5 ♀); slight ↓ in body wt in 1/6 ♂ and 1/5 ♀, severe weight loss in euthanized ♀, ↓ food consumption, ↓ RBC, HB, HCT, ↑MCV, MCH, minimal ↓ in albumin; ↑ liver wt – seen at recovery, ↓ testis weight; immature/degenerated testes 2/4; tubular mineralization, interstitial fibrosis - kidney; aspermia – epididymides; immature seminal vesicle; mineralization of ovary; lymphoid hyperplasia of LN; pigment, macrophage - spleen **360 mg/m²/day:** no deaths; soft feces/diarrhea 1/6 ♂; ↓ RBC, HB, HCT, ↑MCV, MCH; minimal ↓ in albumin; immature/degenerated testes 2/4; tubular mineralization, - kidney; pigment, macrophage - spleen **180 mg/m²/day:** immature/degenerated testes 1/4; tubular mineralization, - kidney; pigment, macrophage - spleen

Toxicology conclusions:

Target organs of imatinib toxicity are epithelial and glandular tissues. Most toxicities appear to be reversible upon cessation of imatinib treatment. The potential interaction of the myelosuppression with the lymphoid tissue effects may be of concern regarding the immune response to infection. Of special concern is the liver toxicity seen in the dog, as this was not reversed by the end of the allotted recovery time. The renal toxicity is also of concern as histopathological evidence occurs without (or before) the clinical chemistry indicators or renal damage.

Histopathology Inventory for NDA # 21-335

Study	007033	987003	007048
Species	Rat	Monkey	Monkey
Adrenals	X*	X*	X*
Aorta	X	X	X
Bone Marrow smear	X	X	X
Bone (femur)	X	X	X
Brain	X*	X*	X*
Cecum	X	X	X
Cervix	X	X	X
Colon	X	X	X
Duodenum	X	X	X
Epididymis	X	X	X
Esophagus	X	X	X
Eye	X	X	X
Fallopian tube			
Gall bladder		X	X
Gross lesions		X	X
Harderian gland	X		
Heart	X*	X*	X*
Ileum	X	X	X
Injection site			
Jejunum	X	X	X
Kidneys	X*	X*	X*
Lachrymal gland	X		X
Larynx			
Liver	X*	X*	X*
Lungs	X	X	X
Lymph nodes, cervical			
Lymph nodes mandibular	X	X	X
Lymph nodes, mesenteric	X	X	X
Mammary Gland	X	X	X
Nasal cavity			
Optic nerves			
Ovaries	X*	X*	X*
Pancreas	X	X	X
Parathyroid	X	X	X
Peripheral nerve			
Pharynx			
Pituitary	X*	X*	X*
Prostate	X*	X*	X*
Rectum	X	X	X
Salivary gland	X	X	X

Sciatic nerve	X	X	X
Seminal vesicles	X	X	X
Skeletal muscle	X	X	X
Skin	X	X	X
Spinal cord	X	X	X
Spleen	X*	X*	X*
Sternum	X	X	X
Stomach	X	X	X
Testes	X*	X*	X*
Thymus	X*	X	X
Thyroid	X*	X*	X*
Tongue	X	X	X
Trachea	X	X	X
Urinary bladder	X	X	X
Uterus	X*	X*	X*
Vagina	X	X	X
Zymbal gland			

X - histopathology performed; * - organ weight obtained

APPEARS THIS WAY
ON ORIGINAL

GENETIC TOXICOLOGY:

Study title: Evaluation of the mutagenic activity of ST1571 D9 in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat).

Key findings: STI571 D9, an intermediate product of STI571, was mutagenic in the *Salmonella typhimurium* reverse mutation assay, but not in the *Escherichia coli* reverse mutation assay.

Study no:	[redacted]271608
Volume #, and page #:	Volume 1.27, page 5-177
Conducting laboratory and location:	[redacted]
Date of study initiation:	30 Aug 1999
GLP compliance:	Compliance included and signed
QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	STI571 D9, lot#992301, 98.7% purity
Formulation/vehicle:	DMSO

Methods:

Strains/species/cell line:	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 *Escherichia coli* strain WP_2uvrA
Dose selection criteria:	
Basis of dose selection:	Highest concentration used in the mutation assay was the concentration from the dose range finding test the concentration that the test substance exhibited limited solubility
Range finding studies:	Conducted with TA100 and WP_2uvrA, with and without activation – with concentrations of 3, 10, 33, 100, 333, 1000, 3330, 5000 µg/plate
Test agent stability:	Stable under storage conditions
Metabolic activation system:	S-9 fraction from [redacted]Wistar rat liver
Controls:	
Vehicle:	DMSO
Negative controls:	DMSO
Positive controls:	TA1535 – sodium azide TA1537 – 9-aminoacridine TA98 – daunomycine TA100 – methylmethanesulfonate WP_2uvrA - 4-nitroquinoline N-oxide With metabolic activation All strains = 2-aminoanthracene
Comments:	Controls were within acceptable historical range
Exposure conditions:	
Incubation and sampling times:	Incubated for 48 hrs then revertant colonies counted
Doses used in definitive study:	10, 33, 100, 333, 1000 µg/plate

Study design: Plate incorporation method

Analysis:

No. of replicates: 3 replicate plates

Counting method: Automatically with a[ ] counter. Manually counted if less than 40 colonies/plate or if sufficient test article precipitate to interfere with the automated system.

Criteria for positive results: 1 – Test article induces a number of revertant colonies, dose related, greater than two-times the number of revertants induced by the solvent control in any of the tester strains, either with or without metabolic activation.

2 – The positive response should be reproducible in at least one independently repeated experiment.

Summary of individual study findings:

Study validity: The negative and positive control values were within the historical control data ranges. Study design and findings are valid.

Study outcome:

Mean number of revertant colonies/3 replicate plates (±S.D.) with STI571 D9 in the *Salmonella typhimurium* mutation assay - TA 1537 strain

Dose (µg/plate)	Without S9 activation		With S9 activation	
	Experiment 1	Experiment 2	Experiment 1	Experiment 2
Positive control	304 ± 69	304 ± 31	448 ± 55	325 ± 8
Solvent control	5 ± 1	6 ± 3	4 ± 1	5 ± 2
10	9 ± 3	12 ± 7	7 ± 4	7 ± 3
33	18 ± 5	18 ± 3	8 ± 1	10 ± 1
100	21 ± 4	30 ± 4	17 ± 4	19 ± 3
333	31 ± 2	36 ± 4	29 ± 6	23 ± 3
1000	40 ± 10	35 ± 6	31 ± 7	27 ± 8

- STI571 D9 is a metabolic intermediate in the manufacturing process of the clinical product, STI571. This intermediate is present in the final product. Because of this, the mutagenic potential of this intermediate product was tested.
- In the *Salmonella typhimurium* strain TA1537 – STI571 D9 produced an 8-fold increase in revertant colonies compared to solvent control. In an independent repeat study, STI571 D9 produced a 6-fold increase in revertant colonies in the TA1537 strain.
- In the presence of S9 activation, STI571 D9 in the TA1537 strain produced a 7.8- and 5.4-fold increase in revertant colonies in the first study and independent repeat, respectively.
- The STI571 intermediate product, STI571 D9, is mutagenic in the *Salmonella typhimurium* reverse mutation assay.

Study title: Evaluation of the mutagenic activity of ST1571 D6 in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat).

Key findings: STI571 D6, an intermediate product of STI571, was mutagenic in the *Salmonella typhimurium* reverse mutation assay, but not in the *Escherichia coli* reverse mutation assay.

Study no:	272036
Volume #, and page #:	Volume 1.27, page 5-203
Conducting laboratory and location:	
Date of study initiation:	30 Aug 1999
GLP compliance:	Compliance included and signed
QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	STI571 D6, lot#992304, 100% purity
Formulation/vehicle:	DMSO

Methods:

Strains/species/cell line:	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 *Escherichia coli* strain WP_2uvrA
Dose selection criteria:	
Basis of dose selection:	Highest concentration used in the mutation assay was the highest concentration from the dose range finding test.
Range finding studies:	Conducted with TA100 and WP_2uvrA, with and without activation – with concentrations of 3, 10, 33, 100, 333, 1000, 3330, 5000 µg/plate
Test agent stability:	Stable under storage conditions
Metabolic activation system:	S-9 fraction from [ ] Wistar rat liver
Controls:	
Vehicle:	DMSO
Negative controls:	DMSO
Positive controls:	TA1535 – sodium azide TA1537 – 9-aminoacridine TA98 – daunomycine TA100 – methylmethanesulfonate WP_2uvrA - 4-nitroquinoline N-oxide With metabolic activation All strains – 2-aminoanthracene
Comments:	Controls were within acceptable historical range
Exposure conditions:	
Incubation and sampling times:	Incubated for 48 hrs then revertant colonies counted
Doses used in definitive study:	100, 333, 1000, 3330, 5000 µg/plate
Study design:	Plate incorporation method

Analysis:

No. of replicates: 3 replicate plates

Counting method: Automatically with a [redacted] counter. Manually counted if less than 40 colonies/plate or if sufficient test article precipitate to interfere with the automated system.

Criteria for positive results: 1 – Test article induces a number of revertant colonies, dose related, greater than two-times the number of revertants induced by the solvent control in any of the tester strains, either with or without metabolic activation.

2 – The positive response should be reproducible in at least one independently repeated experiment.

Summary of individual study findings:

Study validity: Control values were within the historical control data ranges. Study design and findings are valid.

Study outcome:

Mean number of revertant colonies/3 replicate plates (±S.D.) with STI571 D6 in the *Salmonella typhimurium* mutation assay - TA 1537 strain

Dose (µg/plate)	Without S9 activation		With S9 activation	
	Experiment 1	Experiment 2	Experiment 1	Experiment 2
Positive control	304 ± 69	410 ± 87	448 ± 55	194 ± 13
Solvent control	5 ± 1	3 ± 1	4 ± 1	3 ± 2
10	7 ± 3	4 ± 2	6 ± 4	3 ± 1
33	6 ± 2	3 ± 1	6 ± 1	5 ± 2
100	9 ± 3	4 ± 3	6 ± 4	19 ± 2
333	29 ± 5	8 ± 3	26 ± 6	7 ± 2
1000	15 ± 5	3 ± 1	25 ± 7	2 ± 2

Mean number of revertant colonies/3 replicate plates (±S.D.) with STI571 D6 in the *Salmonella typhimurium* mutation assay – With activation

Dose (µg/plate)	TA98 Strain		TA100 Strain	
	Experiment 1	Experiment 2	Experiment 1	Experiment 2
Positive control	1042 ± 69	701 ± 98	933 ± 207	812 ± 76
Solvent control	28 ± 3	18 ± 5	66 ± 4	71 ± 9
3	—	—	80 ± 14	—
10	—	—	82 ± 16	—
33	—	—	108 ± 3	—
100	26 ± 5	23 ± 5	137 ± 24	175 ± 15
333	31 ± 6	35 ± 3	225 ± 22	345 ± 23
1000	31 ± 7	70 ± 8	335 ± 9	477 ± 38
3330	34 ± 9	71 ± 2	212 ± 20	420 ± 19
5000	40 ± 3	66 ± 3	35 ± 14	127 ± 41

- STI571 D6 is a metabolic intermediate in the manufacturing process of the

clinical product, STI571. This intermediate is present in the final product. Because of this, the mutagenic potential of this intermediate product was tested.

- In the *Salmonella typhimurium* strain TA1537 – STI571 D6 produced a 5.8-fold increase in revertant colonies compared to solvent control. In an independent repeat study, STI571 D6 produced a 2.7-fold increase in revertant colonies in the TA1537 strain.
- In the presence of S9 activation, STI571 D6 in the TA1537 strain produced a 6.5- and 3.7-fold increase in revertant colonies in the first study and independent repeat, respectively.
- In the presence of S9 activation, STI571 D6 in the TA98 strain produced a 1.4- and 3.9-fold increase in revertant colonies in the first study and independent repeat, respectively.
- In the presence of S9 activation, STI571 D6 in the TA100 strain produced a 5.1- and 6.7-fold increase in revertant colonies in the first study and independent repeat, respectively.
- The STI571 intermediate product, STI571 D6, is mutagenic in the *Salmonella typhimurium* reverse mutation assay.

Study title: Mutagenicity test using *Salmonella typhimurium* (Batch control).

Key findings: STI571 spiked with the manufacturing intermediates D6 and D9 was not mutagenic in the *Salmonella typhimurium* reverse mutation assay.

Study no:	001815
Volume #, and page #:	Volume 1.27, page 5-229
Conducting laboratory and location:	Novartis Pharma AG, Basel, Switzerland
Date of study initiation:	23 Nov 2000
GLP compliance:	Compliance included but not signed
QA reports:	yes (X) no ( ) – not signed
Drug, lot #, and % purity:	STI571 spiked with intermediates 507-00 (D6) and 508-00 (D9); Batch # MO 00/199
Formulation/vehicle:	DMSO

Methods:

Strains/species/cell line:	*Salmonella typhimurium* strains TA97a, TA98, TA100, TA 102 and TA1535
Dose selection criteria:	
Basis of dose selection:	Highest concentration used in the mutation assay was the highest concentration from the dose range finding test.
Range finding studies:	Conducted with TA100 and WP_2uvrA, with and without activation – with concentrations of 3, 10, 33,

	100, 333, 1000, 3330, 5000 µg/plate
Test agent stability:	Stable under storage conditions
Metabolic activation system:	S-9 fraction from { }rat liver
Controls:	
Vehicle:	DMSO
Negative controls:	DMSO
Positive controls:	TA97a – 9-aminoacridine TA98 – 2-nitrofluorene; benzo(a)pyrene TA100 – sodium azide TA102 – mitomycin C TA1535 – sodium azide With metabolic activation All strains – 2-aminoanthracene
Comments:	Controls were within acceptable historical range
Exposure conditions:	
Incubation and sampling times:	Incubated for 76 hrs then revertant colonies counted
Doses used in definitive study:	100, 333, 1000, 3330, 5000 µg/plate
Study design:	Plate incorporation method
Analysis:	
No. of replicates:	3 replicate plates
Counting method:	Automatically{ } Manually counted if sufficient test article precipitate to interfere with the automated system or other technical reasons.
Criteria for positive results:	1 – Test article produces revertant colonies, in at least one strain in at least one concentration, a response equal to twice (or more) the control incidence. 2 – No repeat study was conducted, as this was a study to confirm earlier findings with another batch of the test compound.

Summary of individual study findings:

Study validity: The negative and positive control values were within the historical control data ranges. Study design and findings are valid.

Study outcome:

- STI571 was spiked with 280 ppm of the D6 intermediate and 180 ppm of the D9 intermediate. These intermediates are present in the final product and limited to 20 ppm D6 and 10 ppm D9. The levels of the intermediates were chosen to show that at levels higher than the human dose would yield, 16 and 8 µg of D6 and D9 uptake daily, that the intermediates are not mutagenic.
- In the *Salmonella typhimurium* strains tested in the conditions of this test, STI571 spiked with the D6 and D9 intermediates, was not mutagenic.

Study title: Oral bone marrow micronucleus test in rats.

Key findings: STI571 D9, an intermediate product of STI571, when administered orally to rats, as not mutagenic when in the micronucleus assay

Study no:	001889
Volume #, and page #:	Volume 1.27, page 5-278
Conducting laboratory and location:	Novartis Pharma AG, Basel, Switzerland
Date of study initiation:	3 Nov 2000
GLP compliance:	Compliance included but not signed
QA reports:	yes (X) no ( ) – not signed
Drug, lot #, and % purity:	STI571 D9; Batch # 0093200026; 99.20% purity
Formulation/vehicle:	Sodium carboxymethylcellulose (CMC)

Methods:

Strains/species/cell line:	[redacted] rats
Dose selection criteria:	
Basis of dose selection:	Based on the dose finding study.
Range finding studies:	Animals were treated twice with 24 hrs between treatments with a high dose of 2000 mg/kg/day by oral gavage. The animals were monitored for signs of toxicity for 4 days. This dose showed no signs of toxicity.
Test agent stability:	Stable under storage conditions for 24 hrs
Metabolic activation system:	None
Controls:	
Vehicle:	Sodium carboxymethylcellulose (CMC)
Negative controls:	Sodium carboxymethylcellulose (CMC)
Positive controls:	Cyclophosphamide (CP)
Comments:	Controls were within acceptable historical range
Exposure conditions:	
Incubation and sampling times:	No incubation. Animals were euthanized 48 hrs after the first of the two doses. Bone marrow cells were collected and slides made for counting. Slides were allowed to dry for 24 hrs before staining.
Doses used in definitive study:	200, 630, 2000 mg/kg/day – dosed again 24 hrs after the first dosing; 5/sex/dose rats
Study design:	Standard rat bone marrow micronucleus test
Analysis:	
No. of replicates:	2 slides made for each rat. Analysis was done on 2000 polychromatic erythrocytes on each slide.
Counting method:	Micronuclei scoring was done automatically by [redacted] analyzer
Criteria for positive results:	1 – Test article induced a micronucleus frequency

statistically significant above control.
2 – Several doses can indicate a drug effect if evidence of a dose-response relationship.
3 – Dose-dependent results, if not statistically significant when compared to control, not considered to be a positive result.

Summary of individual study findings:

Study validity: The negative and positive control values were within the historical control data ranges. Study design and findings are valid.

Study outcome:
- STI571 D9, given orally to rats at doses up to 2000 mg/kg/day, was not mutagenic in the *in vivo* rat bone marrow micronucleus test.
- Frequency of polychromatic erythrocytes, micronucleated polychromatic erythrocytes, and micronucleated normochromatic erythrocytes were not statistically different from controls.

Study title: Mutation assay at the thymidine kinase locus of L5178Y mouse lymphoma cells.

Key findings: STI571 D9, an intermediate product of STI571, is a mutagen at the thymidine kinase locus of L5178Y mouse lymphoma cells

Study no:	001864
Volume #, and page #:	Volume 1.27, page 5-306
Conducting laboratory and location:	Novartis Pharma AG, Basel, Switzerland
Date of study initiation:	7 Nov 2000
GLP compliance:	Compliance included but not signed
QA reports:	yes (X) no ( ) – not signed
Drug, lot #, and % purity:	STI571 D9; Batch # 0093200026; 99.20% purity
Formulation/vehicle:	DMSO

Methods:

Strains/species/cell line: [ ]rats

Dose selection criteria:

Basis of dose selection:	Based on the dose finding study.
Range finding studies:	Doses of 3.125, 6.25, 12.5, 25, 50 and 100 µg/ml
Test agent stability:	Stable under storage conditions for 24 hrs
Metabolic activation system:	S-9 fraction, male Wist rat liver

Controls:

Vehicle:	DMSO
Negative controls:	DMSO
Positive controls:	Methanesulfonic acid methyl ester (MMS) Benzo(a)pyrene
Comments:	Controls were within acceptable historical range

Exposure conditions:

Incubation and sampling times: Scored after 10 days of incubation.
Doses used in definitive study: 4.8, 5.8, 6.9, 8.3 and 10 µg/ml without S9 activation
5.9, 8.9, 13.3., 20 and 30 µg/ml with S9 activation
Study design: Standard thymidine kinase assay in L5178Y mouse lymphoma cells

Analysis:
No. of replicates: 2
Counting method: Scored by eye with a light box
Criteria for positive results: 1 – At least one of the mutant frequencies in the treated groups with acceptable toxicity levels was statistically significantly higher than the solvent-control value.
2 – The linear-trend analysis indicated a significant dose relationship.
3 – The effects were reproducible.

Summary of individual study findings:
Study validity: The negative and positive control values were within normal ranges. Study design and findings are valid.
Study outcome:
- STI571 D9 induced an increased mutant frequency over control. Without S9 activation there was an 11-fold increase over the solvent control. With S9 activation there was a 10.6-fold increase over the solvent control.
- STI571 D9 is a mutagen at the thymidine kinase locus of L5178Y mouse lymphoma cells under the conditions of this study.

Summary of L5178Y Mutagenicity Test

Compound	7	Relative survival %	Relative total Growth	Mutant frequency ($\times 10^{-6}$)	Significance
-S9 (24h Tx)					
DMSO	–	100.00	1.00	96.95	–
MMS	5	56.71	0.61	**1179.82**	*
STI571 D9	4.8	29.65	0.27	407.97	*
	5.8	25.73	0.25	497.58	*
	6.9	18.21	0.16	730.20	*
	8.3	12.30	0.10	1067.08	*
	10	2.59	0.03	1548.40	*
+S9 (3hr Tx)					
DMSO	–	100	1.00	89.06	–
B(a)P	1.5	34.43	0.28	**1451.35**	*
STI571 D9	5.9	98.24	0.91	98.41	NS[a]
	8.9	97.43	0.91	136.99	NS[a]
	13.3	82.58	0.94	173.69	*
	20	50.62	0.35	412.16	*
	30	13.73	0.10	941.32	*

[a]Not significant; * $p < 0.05$

Study title: CGP 53715: Gene mutation test with Chinese hamster cells V79.

Key findings: CGP 53715 did not induce an increase in mutant when compared to the negative control in the Chinese hamster ovary (CHO) cell assay.

Study no:	946215
Volume #, and page #:	Volume 1.27, page 5-257
Conducting laboratory and location:	[ ] Switzerland
Date of study initiation:	27 Feb 1995
GLP compliance:	Not included
QA reports:	yes ( ) no (X)
Drug, lot #, and % purity:	CGP 53715; Batch # 2; unknown purity
Formulation/vehicle:	DMSO

Methods:

Strains/species/cell line:	V79 Chinese hamster cells
Dose selection criteria:	
Basis of dose selection:	Based on the cytotoxicity in the dose finding study.
Range finding studies:	12 doses ranging from 1.8 to 3704 µg/ml were tested.
Test agent stability:	Stable under storage conditions for 24 hrs
Metabolic activation system:	S-9 fraction, from [ ] rat liver
Controls:	
Vehicle:	DMSO
Negative controls:	DMSO
Positive controls:	N-Nitrosodimethylamine – with metabolic activation Ethylmethansulfonate – without metabolic activation
Comments:	Controls were within acceptable historical range
Exposure conditions:	
Incubation and sampling times:	Incubated for 7-8 days after cell washing.
Doses used in definitive study:	1.81, 3.62, 7.23, 14.47, 28.94, and 57.88 µg/ml without S9 activation 28.94, 57.88, 115.75, and 231.5 µg/ml with S9 activation
Study design:	V79 Chinese hamster cell assay
Analysis:	
No. of replicates:	4 with activation – 2 without activation
Counting method:	Scored by eye with a light box
Criteria for positive results:	1 – The assay is valid. 2 – The mutant frequency at one or more concentrations is increased by a factor of 2.5 or more compared to that of the negative control and the number of normalized mutant clones in the treated and untreated cultures differs by more than 20.

Summary of individual study findings:

Study validity: The negative and positive control values were within normal ranges. Study design and findings are valid.

Study outcome:

- The highest concentration tested in the mutagenicity assay with activation caused an acute toxicity of 37.8%. The highest concentration tested without activation caused an acute toxicity of 85.3%.
- In the presence and absence of activation, there was no increase in mutant frequency from treatment with CGP 53715 when compared to the negative control, both after 6-TG and ouabain selection, in this assay under these conditions and concentrations.

Genetic toxicology summary:

Positive results were seen in studies with metabolic activation, at the highest dose tested, in the Chinese hamster ovary study that was reviewed with the original IND. The dose tested, 125 µg/ml, was the dose in which between 51-58% suppression of mitotic activity was seen. This dose did produce significant toxicity, and cytotoxicity itself is mutagenic in this system. This does not exclude these results, however, as maximum suppression of 70-90% is considered optimal for detecting mutagenicity with a cytotoxic compound. In this test, the suppression of 51-58% is below that limit at which any mutations would be due to the cytotoxic effects of imatinib.

Imatinib was tested in an Ames assay, mouse lymphoma assay and rat micronucleus assay. In each of these tests, imatinib yielded non-mutagenic response. However, there are two intermediate products that are also present in the final drug product, STI571 D6 and STI571 D9, that were also tested for mutagenic potential. Both intermediates were positive mutagens in the *Salmonella typhimurium* reverse mutation assay. STI571 D9 was also tested in the mouse lymphoma and rat micronucleus assays. Results of these tests showed STI571 D9 to be a mutagen at the thymidine kinase locus of L5178Y mouse lymphoma cells. An additional Ames assay, conducted with STI571 spiked with D6 and D9, was negative.

Genetic toxicology conclusions:

Based on the Chinese hamster ovary study that was reviewed with the original IND, imatinib was positive for clastogenicity. Positive mutagenic responses were seen with the two intermediate STI571 products tested.

Summary of Results of Genetic Toxicology Studies For Imatinib			
Type of Study	**Compound Used**	**Activation**	**Results**
Ames test	STI571	---	Negative
		S9	Negative
	STI571 D6	---	Positive
		S9	Positive
	STI571 D9	---	Positive
		S9	Positive
	STI571 spiked with D6 and D9	---	Negative
		S9	Negative
Bone marrow micronucleus assay	STI571	---	Negative
	STI571 D9	---	Negative
Mouse lymphoma assay	STI571	---	Negative
		S9	Negative
	STI571 D9	---	Positive
		S9	Positive
Chinese hamster cell assay	STI571	---	Negative
		S9	Positive
	CGP 53715	---	Negative
		S9	Negative

Labeling recommendations:

Label should state that either imatinib mesylate, or one of two intermediate products, have tested positive in the Ames assay, the mouse lymphoma assay, or the Chinese hamster ovary cell assay.

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CARCINOGENICITY:

No carcinogenicity studies included.

Labeling Recommendations:
Label should state that no carcinogenicity studies have been performed with imatinib mesylate.

REPRODUCTIVE TOXICOLOGY:

Study title: CGP 571488: An oral study for effects on fertility and early embryonic development in rats.

Key study findings: NOAEL for both male and female rats, fertility parameters, and embryonic parameters was 20 mg/kg in this study. The high dose of 60 mg/kg significantly impaired sperm motility, testicular and epididymis weights, and body weight gains in the male rats. In the female rats, the high dose administration increased the number of post-implantation loss, and reduced the number of live fetuses and the weight gain during gestation.

Study no.:	Test 974046
Volume #, and page #:	Volume 1.28, page 5-1
Conducting laboratory and location:	Novartis Pharmaceuticals Corp., Summit, NJ
Date of study initiation:	June 1997
GLP compliance:	Compliance included and signed
QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	CGP 57148B, lot# 820296, 98.9% pure
Formulation/vehicle:	Purified water, USP

Methods:

Species/strain:	Rat/Sprague Dawley
Doses employed:	0, 6, 20 and 60 mg/kg/day
Route of administration:	Oral gavage; 10 mL/kg
Study design:	Segment I Study **Females** – dosed daily for 14 days before mating, throughout mating, and through to gestation day (GD) 6 C-sectioned on GD 13 **Males** – dosed daily for 70 days before mating, throughout mating, until sacrifice
Number/sex/group:	24/sex/group —
Parameters and endpoints evaluated:	**Females** – at GD 13 – combined weight of uterus, uterine contents, ovaries and oviducts. Corpora lutea count from both ovaries. Number of implantation sites, viable embryos and resorptions in each uterine horn. Rate of pregnancies also calculated. **Males** – testes and epididymides weight. Testicular sperm counts

Results:

Mortality:	One control and one MD ♂ died during the study
Clinical signs:	**Salivation** – ♂ 13/24 MD rats; 23.24 HD ♀ 3/24 MD rats; 17/24 HD rats **Chromodacryorrhea** – ♂ 5/24 HD rats; ♀ 1/24 HD rats **Staining in mouth/nose** – ♂ 3/24 HD rats; ♀ 1/24 HD rats
Body weight:	Weight Gain in ♂ Rats – High Dose Compared to Control Days 59-63 – 66% less weight gain in HD Days 77-80 – 48% less weight gain in HD Days 87-91 – 34% less weight gain in HD Weight gain in ♀ Rats – HD Compared to Control GD 0-3 – 14% less weight gain in HD GD 3-6 – 28% less weight gain in HD GD 9-13 – 16 % less weight gain in HD *female rat data not statistically significant
Food consumption:	GD 3-6 – HD females – 9% ↓ in food consumed compared to control
In-life observations:	Number animals mated and number of pregnant females comparable across groups Precoital interval and estrous cyclicity comparable across groups
Terminal and necroscopic evaluations:	Resorptions – HD 1788% ↑ over controls Live fetuses - HD 56% ↓ from controls Testes weight – HD 11% ↓ from controls Epididymal weight – HD 12% ↓ from controls Sperm motility – HD 10% ↓ from controls Sperm count – no differences

Summary of individual study findings:

The doses used in this study were chosen based on the results from toxicology studies with oral administration of CGP 57148B for 2 and 13-week periods in the rat. The high dose tested in this study, 60 mg/kg, was expected to produce reproductive effects in both the male and female rats based on previous findings with this dose. In toxicology tests, increased ovary weight, hemorrhagic corpora lutea, adrenocortical hypertrophy and decreased prostate weights were seen at the 60 mg/kg dose.

The 6 and 20 mg/kg doses had no effect on reproductive parameters in either the male or female rats. The high dose, 60 mg/kg, impacted a variety of parameters. In male rats, the HD led to decreases in both testes and epididymal weights. The percent of sperm that were motile was also decreased at this dose. This dose also caused sporadic decreases in weight gain in the male rats. In the female rats, CGP 57148B did not interfere with female rats becoming pregnant. At the HD level it did, however, lead to an increase in embryonic death, and therefore a decrease in the number of viable fetuses. The HD females also had a decrease in weight gain during a period of the gestational phase. The MD level of 20 mg/kg is considered to be the NOAEL for both the male and female fertility parameters as well as for early embryo development.

Study title: CGP 5714813: A Study for Effects on Embryo and Fetal Development in Rats.

Key study findings: The LD and MD of 10 and 30 mg/kg had no impact on maternal weight gain, the ability of the dams to get pregnant, fetal body weights, or fetal visceral exams. The MD dose fetuses had an increased incidence of shortened ribs. The HD of 100 mg/kg significantly increased fetotoxicity and was teratogenic.

Study no.:	Test 966086
Volume #, and page #:	Volume 1.29, page 5-1
Conducting laboratory and location:	Novartis Crop Protection, Toxicology/Experimental Toxicology, Stein, Switzerland
Date of study initiation:	September 1996
GLP compliance:	Compliance included and signed
QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	CGP 57148B, lot# 800395, 99.8% pure
Formulation/vehicle:	0.5% (w/w) aqueous solution of Klucel HF and 0.1% (w/w) polysorbate 80

Methods:

Species/strain:	Rat/1 (SPF) hybrids of RII/1 x RII/2
Doses employed:	0, 10, 30, and 100 mg/kg/day
Route of administration:	Oral gavage; 10 mL/kg
Study design:	Segment II Study **Females** – dosed daily during gestation – from gestational days (GD) 6-15 **Males** – not dosed
Number/sex/group:	24 ♀/group
Parameters and endpoints evaluated:	**Females** Clinical observations, mortality, maternal body weights and food consumption, # corpora lutea/ovary, weight of uterus + contents, # and position of live and dead fetuses, # of implantation sites, # and position of early and late embryo/fetal losses, individual weights and sex of live fetuses, external observations of live fetuses, skeletal and visceral exams of fetuses.

Results:

Maternal toxicity:

Mortality:	One HD ♀ died – GD 7 – caused by gavage error
Clinical signs:	19/23 HD ♀ - discomfort after dosing on GD 14 and 15
Body weight:	HD dams – HD rats gained 15% less weight than controls from GD 16 until day 21 – due to fetal loss Body weight at end of study – gravid uterus weight = carcass weight - carcass weights comparable across dose groups
Food consumption:	HD dams – food consumption decreased during dosing

compared to controls
HD – GD 6-11 – 14% ↓ in food eaten compared to control
HD – GD 11-16 – 12% ↓ in food eaten compared to control

In-life observations: No drug-related effects on number of females impregnated

Terminal and necroscopic evaluations:

Dams:
No drug-related effects on number of implantation sites
↑ post-implantation loss in HD – 233% over control
mostly due to 200%↑ over control in early resorptions
Gravid uterus weights in HD 14% ↓ than control (due to reduced fetal weight and post-implantation loss)
5 litters in HD group with 5 dead fetuses
5 litters in HD group with reduced live litter size (4-9)
Mean # of live fetuses – HD 11%↓ than control

Offspring:
Mean fetal body weight – HD 20%↓ than control

External exam
HD fetuses – 38 from 16 litters with external exam findings
23/292 with exencephaly and/or protruding tongue (11/23 litters)
25/292 with protruding tongue (10/23 litters)
10/292 with encephalocele (6/23 litters)
3 with cleft lip (2/23 litters)
3 with generalized edema (10/23 litters)

Visceral exam
HD fetuses - ↑ incidence of accessory lobulet to the liver (16/119 fetuses; 10/23 litters)

Skeletal exam
MD fetuses
153/153 fetuses with skeletal variations (22/22 litters)
15/153 fetuses with shortened ribs (7/22 litters)

HD fetuses
32/168 fetuses with skeletal malformations (12/23 litters)
20/168 fetuses with absent parietal bone (8/23 litters)
20/168 fetuses with absent frontal bone (8/23 litters)
10/168 fetuses with reduced frontal bone (5/23 litters)
161/168 fetuses with skeletal anomalies (23/23 litters)
23/168 fetuses – bipartite occipital bone (7/23 litters)
22/168 fetuses – wide fontanel (9/23 litters)
135/168 fetuses – irregular ossification occipital bone (23/23 litters)
6/168 fetuses – bipartite sternebra-6 (6/23 litters)
19/168 fetuses – asymmetrically shaped sternebra-6 (14/23 litters)
28/168 fetuses – asymmetrically shaped sternebra-5 (16/23 litters)

15/168 fetuses – asymmetrically shaped sternebra-4 (11/23 litters)
11/168 fetuses – asymmetrically shaped sternebra-3 (10/23 litters)
10/168 fetuses – asymmetrically shaped sternebra-2 (7/23 litters)
28/168 fetuses – fused sternebra-1 and sternebra-2 (16/23 litters)

168/168 fetuses with skeletal variations (23/23 litters)
9/168 fetuses – poor ossification sternabra-5 (7/23 litters)
10/168 fetuses – absent ossification sternabra-5 (9/23 litters)
163/168 fetuses – absent ossification calcaneus (23/23 litters)
110/168 fetuses – absent ossification metatarsal-1 (23/23 litters)
24/168 fetuses – dumbbell-shaped cervical vertebrae centers (11/23 litters)
29/168 fetuses – shortened ribs (15/23 litters)
42/168 fetuses – absent ossification proximal phalanx (anterior digit 2) (16/23 litters)
47/168 fetuses – absent ossification proximal phalanx (anterior digit 5) (16/23 litters)
17/168 fetuses – poor ossification proximal phalanx (anterior digit 5) (11/23 litters)
81/168 fetuses – absent ossification proximal phalanx (posterior digit 2) (22/23 litters)
77/168 fetuses – absent ossification proximal phalanx (posterior digit 3) (19/23 litters)
95/168 fetuses – absent ossification proximal phalanx (posterior digit 4) (22/23 litters)
134/168 fetuses – absent ossification proximal phalanx (posterior digit 5) (23/23 litters)

Significant increase in total litter incidence of skeletal malformations at the HD, 12/23 litters, over control, 1/24 litters. Significant increase in total litter incidence of malformations at the HD, 16/23 litters, compared to control, 1/24 litters.

Summary of individual study findings:

The doses in this study were based on a dose range finding study reviewed in IND[ ] (Test No. 966085). The high dose of 100 mg/kg of CGP 57148B was chosen because in the range finding study this dose yielded maternal toxicity based on discomfort and hemorrhagic discharge in the perineal area and decreased food consumption. This dose also caused post-implantation loss, significant decreases in fetal body weight, and fetal teratogenicity in the form of exencephaly.

Minimal maternal toxicity at the 100 mg/kg was also seen in this study. Over 80% of the rats exhibited signs of discomfort following drug administration. The HD rats consumed less food than controls during the dosing period. The decreased body weight gain during the post-treatment period in the HD group is accounted for by the post-implantation fetal loss. When the weight of the gravid uterus is factored out of the body weight, there is no significant difference across groups.

The LD group in this study was statistically comparable to the control group in maternal parameters, reproductive effects and fetal development. No effect of the MD of CGP 57148B was seen on the maternal parameters, post-implantation loss, or fetal weights. There were 3/298 fetuses, all from the same litter, with protruding tongue. The fact that this was seen in only one litter does not indicate teratogenicity at that dose level. There were 15/153 pups with the skeletal variation of shortened ribs. The incidence of fetal skeletal variations was 100% in all groups, including control. The incidence of the shortened ribs in the MD fetuses was statistically significant over the control group.

The HD level of CGP 57148B was clearly teratogenic. It was also fetotoxic, as there was a significant increase in post-implantation loss and decrease in viable fetuses. The live fetuses of the HD rats were also significantly smaller in body weight than the control group. External exam of these fetuses indicated significant increases over control in the incidence of exencephaly, encephalocele, and protruded tongue. Visceral exams were relatively normal, except for the increased incidence of accessory lobulet in the liver. The skeletal exams of the HD fetuses yielded numerous incidences of skeletal malformations and anomalies. Treating female during organogenesis, GD 6-15, with 100 mg/kg of CGP 57148B is fetotoxic and is teratogenic to the surviving offspring.

Study title: GP 5714813: A Study for Effects on Embryo and Fetal Development in Rabbits.

Key study findings: None of the doses tested significantly increased the incidence of external or visceral exam findings. Skeletal malformations and anomalies were not affected by the drug treatment. Only an increase in one skeletal variation could be associated with the high dose drug treatment.

Study no.:	Test 966088
Volume #, and page #:	Volume 1.30, page 5-1
Conducting laboratory and location:	Novartis Crop Protection, Toxicology/Experimental Toxicology, Stein, Switzerland
Date of study initiation:	September 1996
GLP compliance:	Compliance included and signed

QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	CGP 57148B, lot# 800395, 99.8% pure
Formulation/vehicle:	0.5% (w/w) aqueous solution of Klucel HF and 0.1% (w/w) polysorbate 80

Methods:

Species/strain:	Rabbit/NZW
Doses employed:	0, 6, 20, and 60 mg/kg/day
Route of administration:	Oral gavage; 4 mL/kg
Study design:	Segment II Study **Females** – dosed daily during gestation – from gestational days (GD) 7-19 **Males** – not dosed
Number/sex/group:	20 ♀/group
Parameters and endpoints evaluated:	**Females** Clinical observations, mortality, maternal body weights and food consumption, # corpora lutea/ovary, weight of uterus + contents, # and position of live and dead fetuses, # and position of early and late embryo/fetal losses, individual weights and sex of live fetuses, external observations of live fetuses, skeletal and visceral exams of fetuses.

Results:

Mortality:	No treatment-related deaths
Clinical signs:	No-treatment-related clinical signs
Body weight:	MD rabbits – averaged ↓6% in maternal body weights starting at GD 23 HD rabbits – averaged ↓6% in maternal body weights starting at GD 21
Food consumption:	MD rabbits – averaged ↓21% in food consumption GD 12 -20 HD rabbits – averaged ↓22% in food consumption GD 7 -20
In-life observations:	No treatment-related effects on: Fetal loss – pre- and post-implantation Number of implantations Number of live fetuses Sex ratio of fetuses Fetal body weights
Terminal and necroscopic evaluations:	
Dams:	No treatment-related effects on gravid uterine weights No treatment-related necroscopic effects
Offspring:	No treatment-related external fetal effects No treatment-related visceral fetal effects

No-treatment-related skeletal malformations
No treatment-related skeletal anomalies
Only significant skeletal variation
HD - 15/103 fetuses – incidence of sutural bones (due to slight delay in ossification) (11/16 litters)

Summary of individual study findings:

The doses in this study were chosen based on a range finding study reviewed in IND)(Test No. 966087). The MD dose of 30 mg/kg of CGP 57148B was tolerated well with only a significant decrease in food consumption seen from GD 7-16. The HD in that study, 100 mg/kg, was lethal in 1/7 animals. There was total implantation loss in 4/6 of the remaining litters.

Maternal toxicity of the HD in this study was considerably less than in the dose range finding study. No clinical signs of toxicity were seen. Decreased food and body weights were the only drug-related maternal toxicity seen. No fetotoxicity was seen in this study.

The ability to become pregnant, maintain pregnancy and have viable fetuses was not impacted in rabbits by CGP 57148B. The majority of the fetal parameters were not affected by the drug either. A significant increase in one skeletal variation, indicative of a slight delay in fetal development, was seen in the 60 mg/kg dose. This delay in development could not have been too severe, as the fetal body weights were not affected by this dose when compared to the control animals.

Reproductive toxicology summary:

When administered to female rats and rabbits, imatinib had a clear embryo-fetal toxic effect. When administered to rats either prior to mating through to gestational day (GD) 6 or during gestation from GD 6-15, significant post-implantation fetal loss is noted, due mostly to early resorptions. This was seen at doses as low as 360 mg/m^2/day. When dosing pregnant rabbits from GD 7-19, post-implantation loss was seen at a dose of 1200 mg/m^2/day, the HD used in a study reviewed in the initial IND. This was not seen at the HD in the experiment reviewed here, 720 mg/m^2/day.

When imatinib was administered to male rats, fertility was not impaired. However, testis and epididymal weights were decreased at the HD of 360 mg/m^2/day, as was sperm motility. Sperm counts were not affected by the doses tested, up to 360 mg/m^2/day. A segment I study in rabbits was not conducted.

The teratogenic potential of imatinib was investigated in both rat and rabbit studies. In the rat, there was a slight indication of teratogenicity at the MD of 180 mg/m^2/day. Skeletal variations were seen in 100% of the litters, including control. The MD litters had a significant increase of the skeletal variation of shortened ribs when compared to control. When imatinib was administered to pregnant rats from GD 6-15, the HD of 600 mg/m^2/day was clearly teratogenic. Increased incidences of skeletal malformations, anomalies and variations were seen when comparing the offspring of this dose group to control fetuses. Significantly lower fetal body weights were also seen following maternal administration of 600 mg/m^2/day. Evidence of

teratogenicity in the rabbit has not been observed with imatinib, with doses up to 1200 mg/m^2/day.

Reproductive toxicology conclusions:

Imatinib mesylate clearly impacts the ability of rats and rabbits to carry fetuses to term, based on the significant incidence of fetal loss due to early resorptions. The teratogenic potential of imatinib to surviving fetuses was demonstrated in the rat studies.

Labeling recommendations:

Women should be advised against becoming pregnant or breastfeeding while taking Gleevec®.

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SPECIAL TOXICOLOGY STUDIES:

Study title: ST1571 Single-dose oral mechanistic toxicity and safety pharmacology study in dogs.

Key study findings: STI571 had no cardiac or respiratory adverse effects. The only treatment-related effect seen was salivation and vomiting.

Study no:	Test 001091
Volume #, and page #:	Volume 1.27, page 5-100
Conducting laboratory and location:	• Toxicology/Pathology, Novartis Pharma AG, Basel, Switzerland • Drug Metabolism and Pharmacokinetics, Novartis Pharmaceuticals Corp., East Hanover, NJ
Date of study initiation:	27 Sep 2000
GLP compliance:	Included but not signed
QA reports:	yes (X) no ( ) Included but not signed
Drug, lot #, and % purity:	STI571, lot# 9923006, 100% purity
Formulation/vehicle:	Empty gelatin capsules

Methods: Beagle dogs, N=4, were given gelatin capsules of the test compound followed by the control, once daily, with five days between treatments.

Dosing: 0, 100 mg/kg

Observations and times:

- Mortality and clinical signs were monitored daily.
- Body weights were taken prior to dosing.
- Electrocardiography was performed before and 1, 2, 4, 7, and 24 hrs post administration of the control and test compound.
- Systolic arterial bp, respiration rate and depth, and rectal body temperature were monitored before and 1, 2, 4, 7, and 24 hrs post administration of the control and test compound.
- Toxicokinetics performed on blood samples obtained after test compound administration.
- Animals euthanized one day after test compound administered.
- Immunochemistry performed to detect autoantibodies in serum and numerous organ tissue samples.

Results: No mortality
Salivation (4/4) and vomiting (3/4) after STI571
No treatment-related effects on body weight
Heart rate slightly higher following STI571, but still within normal range and HR was slightly higher pre-administration that day.
No treatment-related changes in systolic arterial blood pressure
No treatment-related changes in respiration rate and depth
No treatment-related changes in rectal body temperature
No treatment-related macroscopic findings at necropsy
Autoantibody labeling in the hepatocytes of STI571 dogs when blood from previously STI571-treated dogs was used. The autoantibody detection was comparable to that of the livers of non-treated dogs.

Summary of individual study findings:

Single oral administration of STI571 to dogs had no adverse effects on cardiac or respiratory parameters or rectal body temperature. Using the procedures of this test, there do not appear to be changes in the dog liver induced by the STI571 administration.

Conclusions:

This special toxicology study was conducted to further investigate the liver toxicity that has been seen with imatinib mesylate administration to dogs. This adverse effect is important to note, as not only did it not reverse during the recovery period, but also it appeared to increase in severity. This study did not show any imatinib-induced changes in the liver. The autoantibodies detected in the liver of dogs following a single oral dose of 2000 mg/m^2, when using the serum of dogs treated for 4 weeks with 2000 mg/m^2, was comparable to the autoantibody labeling in the hepatocytes of dogs never treated with imatinib. The autoantibodies may be recognizing a native structure of a protein in the liver of these dogs.

ADDENDUM TO REVIEW:
None

APPENDIX/ATTACHMENTS:
None

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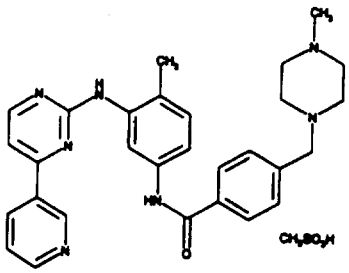
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number:	21-335
Review number:	2
Serial number/date/type of submission:	000/27 February 2001/NDA
Information to sponsor:	Yes (X) No ( )
Sponsor and/or agent:	Novartis Pharmaceuticals Corporation
Manufacturer for drug substance :	Novartis Ringaskiddy Ltd.
Reviewer name:	Kimberly A. Benson, Ph.D.
Division name:	Division of Oncological Drug Products
HFD #:	150
Review completion date:	4 May 2001

Drug:

Trade name:	Gleevec™
Generic name:	Imatinib mesylate (Pending)
Code name:	STI571; CGP 57148B
Chemical name:	4-[4-(Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]-benzamide methanesulfonate
CAS registry number:	220127-57-1 [152459-95-5 for the free base]
Mole file number:	None
Molecular formula/ weight:	$C_{30}H_{35}N_7SO_4$/589.7
Structure:	

Relevant INDs:

Drug class: Protein-tyrosine kinase inhibitor

Indication: For the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failing interferon-alpha therapy.

Clinical formulation:

Ingredient	Amount (mg)
STI571 mesylate	[redacted]
Microcrystalline cellulose	
Crospovidone	
Colloidal Silicon Dioxide	
Magnesium stearate	

Route of administration: Oral tablets

Proposed use: For the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failing interferon-alpha therapy. The recommended dosage is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. The prescribed dose should be administered orally, once daily with a meal and a large glass of water. Treatment should be continued as long as the patient continues to benefit. Dose increase from 400 mg to 600 mg in patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in patients in accelerated phase or blast crisis may be considered.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

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2 pages redacted from this section of the approval package consisted of draft labeling

Draft Labeling

4. Nursing Mothers

Sponsor's proposed wording:

Draft labeling

Suggested modifications:

Draft LABeling

RECOMMENDATION: The pharmacology/toxicology data supports approval of Gleevec® for chronic myeloid leukemia.

/S/ /S/

Kimberly A. Benson, Ph.D. Date
Pharmacologist

John K. Leighton, Ph.D., DABT Date
Pharmacology/Toxicology Team Leader